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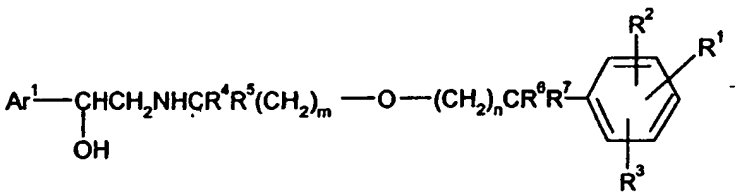
(54) Title: MEDICINAL COMPOUNDS



(I)

(57) Abstract: The present invention relates to novel compounds of formula (I), to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use in the prophylaxis and treatment of respiratory diseases.

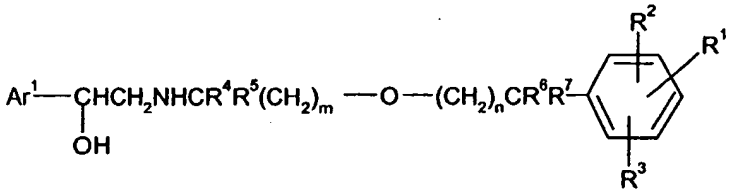
Medicinal Compounds

The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2-adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine compounds including 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

Although salmeterol and the other commercially available β_2-adrenoreceptor agonists are effective bronchodilators, the duration of action is approximately 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2-adrenoreceptors and having an advantageous profile of action.

According to the present invention, there is provided a compound of formula (I)



(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;
n is an integer of from 2 to 10, preferably from 2 to 6;
with the proviso that m + n is 5 to 19, preferably 5 to 12;

R^1 is selected from hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6} alkoxy, cyano, nitro, halo,

C_{1-6}haloalkyl, -$XNR^8C(O)R^9$, -$XNR^8C(O)NR^9R^{10}$, –$XNR^8C(O)NC(O)NR^9R^{10}$, -$XNR^8SO_2R^9$, -$XSO_2NR^9R^{10}$, XSR^8, $XSOR^8$, XSO_2R^8, -XNR^9R^{10}, -$XNR^8C(O)OR^9$, $XNR^8SO_2NR^9R^{10}$, XCO_2R^{10}, or -$XC(O)NR^9R^{10}$;

or R^1 is selected from -X-aryl, -X-hetaryl, or -X-(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, cyano, nitro, $CONR^9R^{10}$, -$NR^8C(O)R^9$, SR^8, SOR^8, -SO_2R^8, -$SO_2NR^9R^{10}$, -CO_2R^{10}, -NR^9R^{10}, or hetaryl optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, or C_{1-6}haloalkyl;

X is –$(CH_2)_r$- or C_{2-6} alkenylene;

r is an integer from 0 to 6, preferably 0 to 4;

R^8 and R^9 are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6}alkyl)- and aryl(C_{1-6}alkyl)- and R^8 and R^9 are each independently optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, -NHC(O)(C_{1-6}alkyl), -SO_2(C_{1-6}alkyl), -SO_2(aryl), -CO_2H, and -CO_2(C_{1-4}alkyl), -NH_2, -NH(C_{1-6}alkyl), aryl(C_{1-6}alkyl)-, aryl(C_{2-6}alkenyl)-, aryl(C_{2-6}alkynyl)-, hetaryl(C_{1-6}alkyl)-, -$NHSO_2$aryl, -NH(hetarylC_{1-6}alkyl), -$NHSO_2$hetaryl, -$NHSO_2$(C_{1-6}alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

or R^8 and R^9, together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered nitrogen – containing ring;

or where R^1 is –$XNR^8C(O)NR^9R^{10}$, R^8 and R^9 may, together with the -NC(O)N- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an imidazolidine ring, such as imidazolidine-2,4-dione;

or where R^1 is –$XNR^8C(O)OR^9$, R^8 and R^9 may, together with the -NC(O)O- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an oxazolidine ring, such as oxazolidine-2,4-dione;

R^{10} is selected from hydrogen, C_{1-6}alkyl and C_{3-7} cycloalkyl;

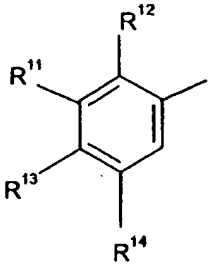
or where R^1 contains a moiety $-NR^9R^{10}$, R^9 and R^{10} may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

R^2 and R^3 are each independently selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo, aryl, aryl(C_{1-6}alkyl)-, C_{1-6}haloalkoxy, and C_{1-6}haloalkyl;

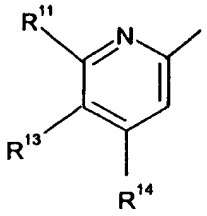
R^4 and R^5 are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4;

one of R^6 and R^7 represents hydrogen or C_{1-4}alkyl and the other of R^6 and R^7 represents C_{1-4}alkyl, or R^6 and R^7, together with the carbon atom to which they are bonded, form a C_{3-7}cycloalkyl ring; and

Ar^1 is a group selected from



(a)



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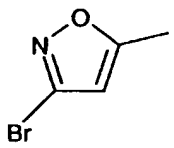
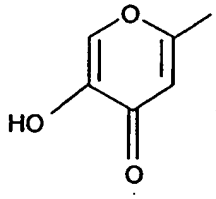


(c)

and



(d)

wherein R^{11} represents hydrogen, halogen, $-(CH_2)_qOR^{15}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}SO_2R^{16}$, $-SO_2NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$,
and R^{12} represents hydrogen, halogen or C_{1-4} alkyl;

or R^{11} represents $-NHR^{18}$ and R^{12} and $-NHR^{18}$ together form a 5- or 6- membered heterocyclic ring;

R^{13} represents hydrogen, halogen, $-OR^{15}$ or $-NR^{15}R^{16}$;

R^{14} represents hydrogen, halogen, haloC_{1-4} alkyl, $-OR^{15}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$;

R^{15} and R^{16} each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$ and $-OC(O)NR^{15}R^{16}$, R^{15} and R^{16} independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

R^{17} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

q is zero or an integer from 1 to 4.

In a particular embodiment the present invention provides a compound of formula (I) as defined hereinabove, or a salt, solvate or physiologically functional derivative thereof, except that R^{11} does not represent hydrogen.

In the compounds of formula (I) the group R^1 is preferably selected from hydrogen, $-XNR^8C(O)NR^9R^{10}$, or $-XSO_2NR^9R^{10}$.

In the definition of X, the term alkenylene includes both *cis* and *trans* structures. Examples of suitable alkenylene groups include –CH=CH-.

X is preferably $(CH_2)_r$, where r is 0 to 2, or C_2-alkenylene.

In the compounds of formula (I) the group R^1 is preferably attached to the meta-position relative to the $-O-(CH_2)_n-$ link.

R^4 and R^5 are preferably independently selected from hydrogen and methyl, more preferably R^4 and R^5 are both hydrogen.

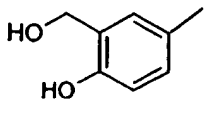
Preferably, one of R^6 and R^7 is selected from hydrogen and methyl and the other of R^6 and R^7 represents methyl.

m is suitably 4, 5, or 6, and n is suitably 2, 3, 4, or 5. Preferably m is 5 or 6 and n is 2 or 3, such that m + n is 7,8 or 9 preferably 8.

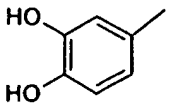
In the compounds of formula (I) the group Ar^1 is preferably selected from groups (a) and (b) above. In said groups (a) and (b), when R^{11} represents halogen this is preferably chlorine or fluorine. $R^{15}$and R^{16} preferably each independently represent hydrogen or methyl. R^{17} preferably represents substituted phenyl. The integer q preferably represents zero or 1. Thus for example $-(CH_2)_qOR^{15}$ preferably represents OH or $-CH_2OH$;
$NR^{15}C(O)R^{16}$ preferably represents $-NHC(O)H$;
$-SO_2NR^{15}R^{16}$ preferably represents $-SO_2NH_2$ or SO_2NHCH_3;
$NR^{15}R^{16}$ preferably represents $-NH_2$;
$-OC(O)R^{17}$ preferably represents substituted benzoyloxy eg. $OC(O)-C_6H_4-(p-CH_3)$; and
$-OC(O)N\ R^{15}\ R^{16}$ preferably represents $OC(O)N(CH_3)_2$.

When R^{11} represents NHR^{18} and together with R^{12} forms a 5- or 6- membered heterocyclic ring $-NHR^{18}-R^{12}-$ preferably represents a group:
$-NH-CO-R^{19}-$ where R^{19} is an alkyl, alkenyl or alkyloxy group;
$-NH-SO_2R^{20}-$ where R^{20} is an alkyloxy group;
$-NH-R^{21}-$ where R^{21} is an alkyl or alkenyl group optionally substituted by $COOR^{22}$ where R^{22} is C_{1-4} alkyl; or
NH-CO-S-;
wherein said alkyl and alkenyl groups and moieties contain 1 or 2 carbon atoms.

Particularly preferred groups (a) and (b) may be selected from the following groups (i) to (xxi):



(i)



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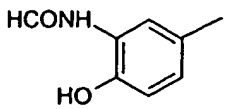

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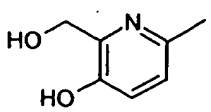

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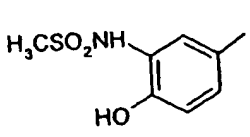

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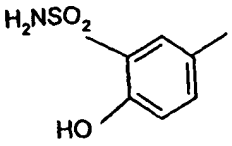

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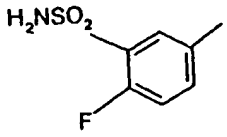

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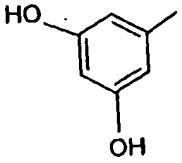

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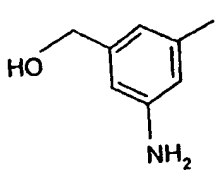

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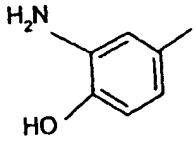

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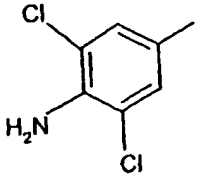

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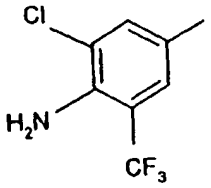

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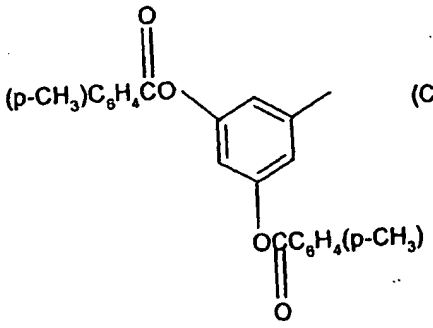

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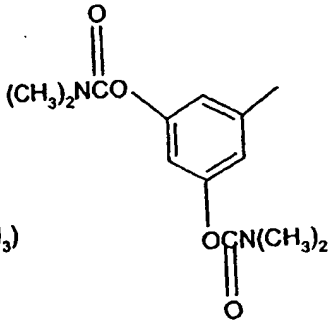

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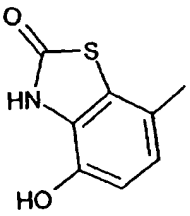

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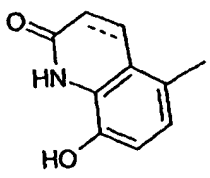

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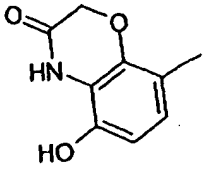

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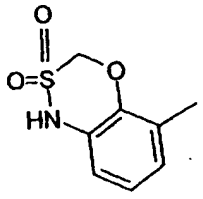

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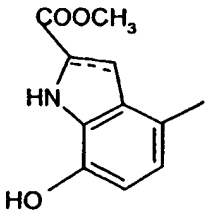

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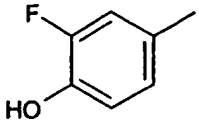

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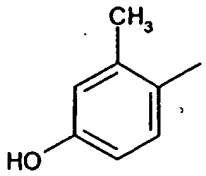
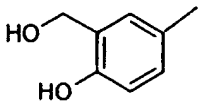


(xxi)

wherein the dotted line in (xvi) and (xix) indicates an optional double bond.

Most preferably Ar^1 is a group (i):



(i)

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Preferred compounds of the invention include:
2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(4-methyl-4-phenylpentyl)oxy]hexyl}amino)ethyl]phenol;
2-(Hydroxymethyl)-4-((1*R*)-1-hydroxy-2-{[6-(2-methyl-2-phenylpropoxy)hexyl]amino}ethyl)phenol;
2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(4-phenylpentyl)oxy]hexyl}amino)ethyl]phenol

and salts, solvates and physiologically functional derivatives thereof.

It will be appreciated that the compounds of formula (I) includes an asymmetric centre, namely the carbon atom of the

group. The compounds may therefore exist in two different enatiomeric forms. The present invention includes both (S) and (R) enantiomers at both chiral centres either in substantially pure form or admixed in any proportions.

Similarly, where R^4 and R^5 are different groups, or where R^6 and R^7 are different groups the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

Thus the compounds of formula (I) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the parent compound of formula (I) for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic, tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl , methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-

benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

Pharmaceutically acceptable esters of the compounds of formula (I) may have a hydroxyl group converted to a C_{1-6}alkyl, aryl, aryl C_{1-6} alkyl, or amino acid ester.

As mentioned above, the compounds of formula (I) are selective β_2-adrenoreceptor agonists as demonstrated using functional or reporter gene readout from cell lines transfected with human beta-adrenoreceptors as described below. Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have shown an improved therapeutic index in animal models relative to existing long-acting β_2-agonist bronchodilators. As such, compounds of the invention may be suitable for once-daily administration.

Compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2-adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease (e.g. rhinitis, including seasonal and allergic rhinitis).

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular, the present invention provides

such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect the present invention provides such a method for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

In the alternative, there is also provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated. In particular, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

The amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered by inhalation at a dose of from 0.0005mg to 10 mg, preferably 0.005mg to 0.5mg, eg. 0.05mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 10mg per day and preferably 0.01mg to 1mg per day, most preferably 0.05mg to 0.5mg per day.

While it is possible for the compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di or poly-saccharides (eg. lactose or starch). Use of lactose is preferred.

Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient.

Alternatively, the compound of the invention may be presented without excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134, US Patent Nos. 6,632,666, 5,860,419, 5,873,360 and 5,590,645 or Diskhaler, see GB 2178965, 2129691 and 2169265, US Patent No.s 4,778,054, 4,811,731, 5,035,237, the disclosures of which are hereby incorporated by reference) or metered in use (eg as in Turbuhaler, see EP 69715 or in the devices described in US Patents No. 6,321,747 the disclosures of which are hereby incorporated by reference). An example of a unit-dose device is Rotahaler (see GB 2064336 and US Patent No. 4,353,656, the disclosures of which are hereby incorporated by reference). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μm, preferably 2-5μm. Particles having a size above 20μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90μm and not less than 15% will have a MMD of less than 15μm.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose an acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having

regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic agent, another β_2-adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide,

ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester and 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, more preferably 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2-adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Of particular interest is use of the compound of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

A method for determining IC_{50}s ratios is set out in US patent 5,998,428 which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/51599 for an another description of said assay.

The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity.

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC_{50} ratio of about 0.1 or greater; said ratio is the ratio of the IC_{50} value for competing with the binding of 1nM of [^{3}H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC_{50} value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[^{3}H]-cAMP as the substrate.

Most preferred are those PDE4 inhibitors which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC_{50} ratio of 0.1 or greater.

Other compounds of interest include:

Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomalast) and its salts, esters, pro-drugs or physical forms;

AWD-12-281 from elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu

Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther,1998, 284(1): 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M_1 and M_2 receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:

Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.

Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

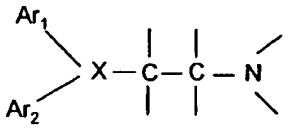
Hyoscyamine (*d*, *l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt-CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also

cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperizine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperizine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: chlropheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a physiologically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

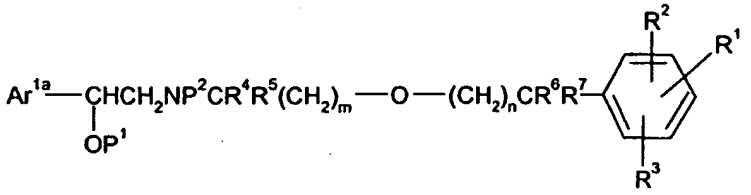
According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I) or a salt, solvate, or physiologically functional derivative thereof which comprises a process as defined below followed by the following steps in any order:

(i) optional removal of any protecting groups;

(ii) optional separation of an enantiomer from a mixture of enantiomers;

(iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

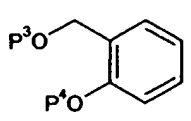
In one general process (a), a compound of formula (I), may be obtained by deprotection of a protected intermediate, for example of formula (II):



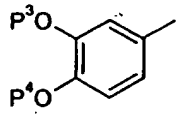
(II)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7, m, and n are as defined for the compound of formula (I), Ar^{1a} represents an optionally protected form of Ar^1; and P^1 and P^2 are each independently either hydrogen or a protecting group, provided that the compound of formula (II) contains at least one protecting group.

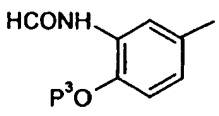
Protected forms Ar^{1a} of the preferred groups Ar^1 may be selected from:



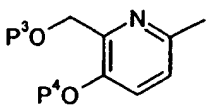
(ia)



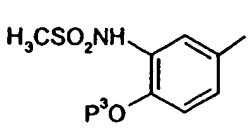
(iia)



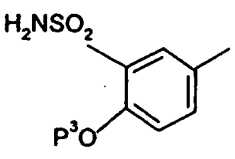
(iiia)



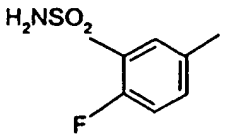
(iva)



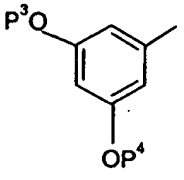
(va)



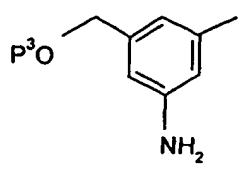
(via)



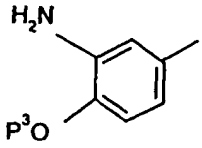
(viia)



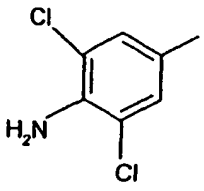
(viiia)



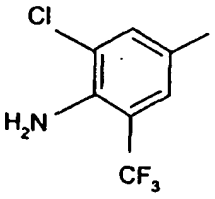
(ixa)



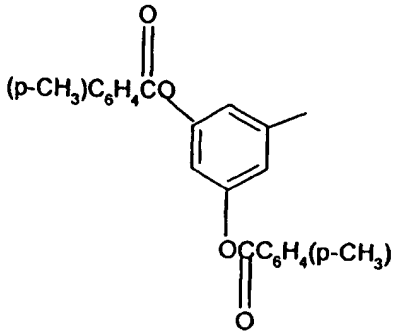
(xa)



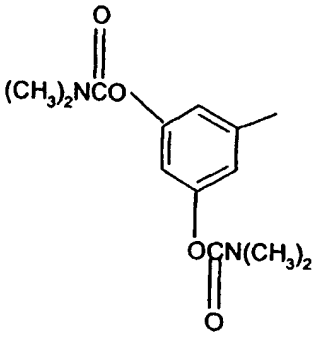
(xia)



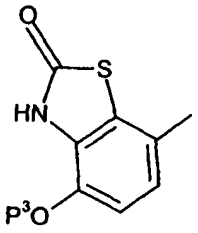
(xiia)



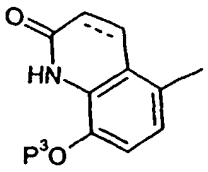
(xiiia)



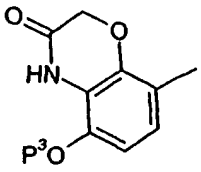
(xiva)



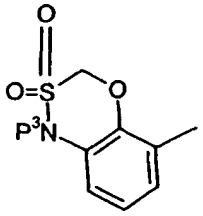
(xva)



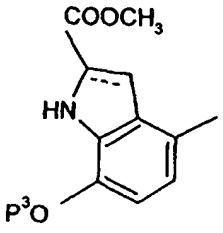
(xvia)



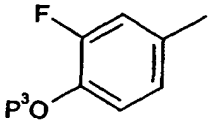
(xviia)



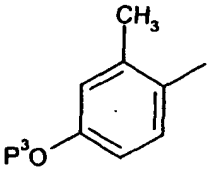
(xviiia)



(xixa)



(xxa)



(xxia)

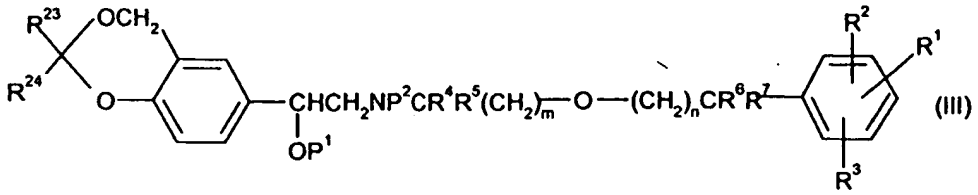
wherein P^3 and P^4 are each independently either hydrogen or a protecting group provided that at least one of P^3 and P^4 is a protecting group, and the dotted line in (xvia) and (xixa) denotes an optional double bond. It will be appreciated that where Ar^1 is a group (vii), (xi), (xii), (xiii) or (xiv) protection is not required.

Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by P^3 and P^4 are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by P^2 include benzyl, α-methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino or hydroxyl function. For example, the –CH(OH) group may be orthogonally protected as $-CHOP^1$ using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene (see above).

The deprotection to yield a compound of formula (I) may be effected using conventional techniques. Thus, for example, when P^3, P^4, and/or P^2 is an aralkyl group, this may be cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

When P^3 and/or P^4 is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by P^2 may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene (see above). In a particular embodiment of process (a), P^3 and P^4 may together represent a protecting group as in the compound of formula (III).



(III)

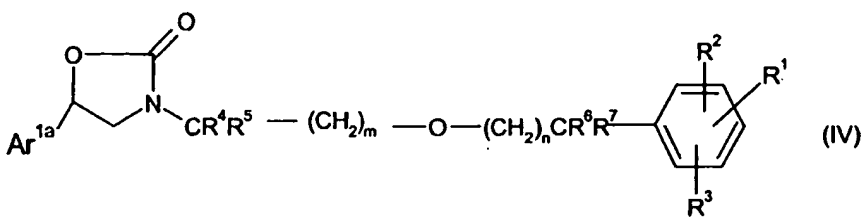
or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, P^1, P^2, m, and n are as defined for the compound of formula (II) R^{23} and R^{24} are independently selected from hydrogen,

C_{1-6}alkyl, or aryl or R^{23} and R^{24} together form a C_{3-7} alkyl group. In a preferred aspect, both R^{23} and R^{24} are methyl.

A compound of formula (III) may be converted to a compound of formula (I) by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketalisation in an alcohol, for example ethanol, in the presence of a catalyst such as an acid (for example, toluenesulphonic acid) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

It will be appreciated that the protecting groups P^1, P^2, P^3 and P^4 (including the cyclised protecting group formed by P^3 and P^4 as depicted in formula (III) may be removed in a single step or sequentially. The precise order in which protecting groups are removed will in part depend upon the nature of said groups and will be readily apparent to the skilled worker. Preferably, when P^3 and P^4 together form a protecting group as in formula (III) this protecting group is removed together with any protecting group on the CH(OH) moiety, followed by removal of P^2.

Compounds of formulae (II) and (III) wherein P^1 and P^2 represent hydrogen may be prepared from the corresponding compound of formula (IV):

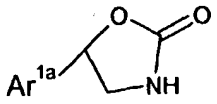


(IV)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, Ar^{1a}, m, and n are as defined for the compound of formula (II) or (III).

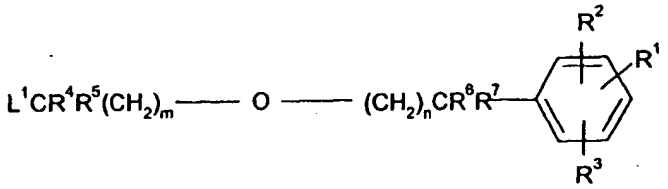
The conversion of a compound of formula (IV) to a compound of formula (II) or (III) may be effected by treatment with a base, for example a non-aqueous base, such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran.

Compounds of formula (IV) may be prepared by coupling a compound of formula (V):



(V)

or a salt or solvate thereof, wherein Ar^{1a} is as defined for the compound of formula (IV) with a compound of formula (VI):



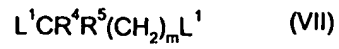
(VI)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, m and n are as defined for the compound of formula (IV) and L^1 is a leaving group, for example a halo group (typically bromo or iodo) or a sulfonate such as an alkyl sulfonate (typically, methanesulfonate), an arylsulfonate (typically, toluenesulfonate), or a haloalkyl sulfonate (typically, trifluoromethanesulfonate).

The coupling of a compound of formula (V) with a compound of formula (VI) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, or an inorganic base such as cesium carbonate, in an aprotic solvent, for example N,N-dimethylformamide or tetrahydrofuran.

Compounds of formula (V) may be prepared for example as described in WO 02/066422.

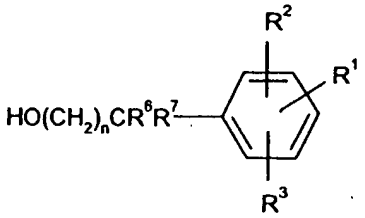
A compound of formula (VI) may be prepared from a corresponding compound of formula (VII):



(VII)

wherein R^4, R^5 and m are as defined for compounds of formula (I) and each L^1 which may be the same or different represents a leaving group, eg. as defined above for compounds of formula (VI);

by reaction with an alcohol of formula (VIII):



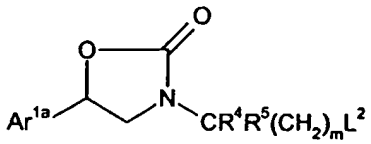
(VIII)

wherein R^1, R^2, R^3, R^6, R^7 and n are as defined for compounds of formula (VI).

The coupling of compounds (VII) and (VIII) may be effected in the presence of an inorganic base, such as aqueous sodium hydroxide, under phase transfer conditions in the presence of an ammonium salt such as tetraalkylammonium bromide.

Compounds of formula (VII) and (VIII) are commercially available or may be prepared by methods known in the art, for example compounds of formula (VIII) may be prepared as described in **J. Org. Chem.**, 1972, **37**, 825.

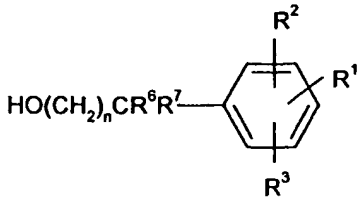
Alternatively, a compound of formula (IV) may be prepared by reacting a compound of formula (IX):



(IX)

wherein Ar^{1a}, R^4, R^5 and m are as defined for compounds of formula (II) and L^2 is a leaving group, such as halo (typically bromo);

with a compound of formula (VIII):



(VIII)

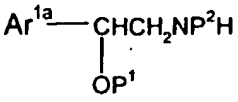
as hereinbefore defined.

The coupling of a compound of formula (IX) with a compound of formula (VIII) may be effected in the presence of a base, such as metal hydride, for example sodium hydride, an alkoxide such as potassium t-butoxide or an inorganic base such as caesium carbonate, in an aprotic solvent, for example dimethylformamide.

A compound of formula (IX) may be prepared by coupling a compound of formula (V) as hereinbefore defined with a compound of formula (VII) as hereinbefore defined, using a method analogous to the coupling of a compound of formula (IX) with a compound of formula (VIII), as described hereinabove.

Compounds of formula (II) or (III) wherein P^2 is hydrogen or a protecting group may be prepared as described in process (b) below.

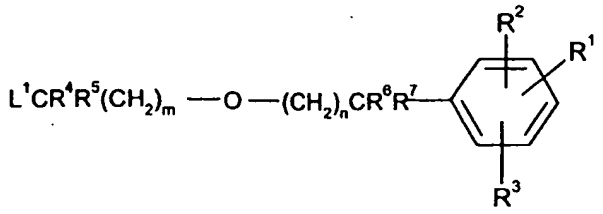
In a further process (b), a compound of formula (I) may be obtained by alkylation of an amine of formula (X):



(X)

wherein P^1 and P^2, are each independently either hydrogen or a protecting group and Ar^{1a} is as hereinbefore defined. Suitable protecting groups are discussed in the definition of compounds of formula (II);

with a compound of formula (VI):



(VI)

as hereinbefore defined, followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II).

The reaction of compounds of formulae (X) and (VI) is optionally effected in the presence of an organic base such as a trialkylamine, for example, diisopropylethylamine, and in a suitable solvent for example dimethyl formamide.

Compounds of formula (X) are known in the art (for example EP-A 0947498B or WO 02/070490) or may be readily prepared by a person skilled in the art.

Further details concerning preparation of compounds (X) wherein Ar^{1a} is a group (va) can be found in DE3524990; concerning the preparation of compounds (X) wherein Ar^{1a} is a group (iia), (viiia), and (xvia) in EP-A-162576; concerning the preparation of compounds (X) wherein Ar^{1a} is a group (iva) in EP-A-220054; concerning the preparation of compounds (X) wherein Ar^{1a} is a group (xia) in GB2165542 and concerning the preparation of compounds (X) wherein Ar^{1a} is a group (c) in GB2230523.

It will be appreciated that in any of the routes described above, the precise order of the synthetic steps by which the various groups and moieties are introduced into the molecule may be varied. It will be within the skill of the practitioner in the art to ensure that groups or moieties introduced at one stage of the process will not be affected by subsequent transformations and reactions, and to select the order of synthetic steps accordingly.

The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating suitable diastereoisomers, or (ii) by direct synthesis from the appropriate chiral intermediates by the methods described above.

Optional conversions of a compound of formula (I) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

Throughout the examples, the following abbreviations are used:

LC: Liquid Chromatography

LCMS: Liquid Chromatography Mass Spectrometry.

RT : retention time

THF : tetrahydofuran

DMF : N,N-dimethylformamide

DCM : dichloromethane

EtOAc : ethyl acetate

Et_2O : diethyl ether

MeOH : methanol

$KOSiMe_3$: potassium trimethylsilanolate

bp : boiling point

ca : circa

h : hour(s)

min : minute(s)

All temperatures are given in degrees centigrade.

Silica gel refers to Merck silica gel 60 Art number 7734.

Flash silica gel refers to Merck silica gel 60 Art number 9385.

Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module.

Bond Elut are prepacked cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian.

NMR experiments at 400MHz (unless specified otherwise).

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 0%B, 5.3-5.5 min 0%B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

Example 1

2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(4-methyl-4-phenylpentyl)oxy]hexyl}amino)ethyl]phenol acetate

i) {4-[(6-Bromohexyl)oxy]-1,1-dimethylbutyl}benzene

A mixture of 4-methyl-4-phenylpentan-1-ol (2.80g)) (J. Org Chem 1972, 37, 825-836), 1,6-dibromohexane (7.25ml) and tetrabutylammonium bromide (101mg) was treated with 50% w/v aqueous sodium hydroxide solution (8ml) and the mixture was vigorously stirred at 20° for 18h. Water (50ml) was added and the mixture was extracted with DCM. The extract was dried (Na_2SO_4) and the solvent evaporated *in vacuo* to give a residual liquid which was purified by flash chromatography on silica gel. Elution with petroleum ether then EtOAc - petroleum ether (40-60°C) (1:9) gave *the title compound* (4.126g). LCMS RT = 4.39min.

ii) (5R)-5-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-3-{6-[(4-methyl-4-phenylpentyl)oxy]hexyl}-1,3-oxazolidin-2-one

A solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (2.73g) (WO 02/066422) in DMF (25ml) under nitrogen was treated with sodium hydride (60% dispersion in mineral oil, 526mg) and the mixture stirred at 20° for 15min. A solution of {4-[(6-bromohexyl)oxy]-1,1-dimethylbutyl}benzene (4.117g) in DMF (5ml) was added and the mixture was stirred at 20° for 3h. Phosphate buffer solution (pH 6.5, 25ml) and water (50ml) were added and the mixture was extracted with EtOAc. The extract was washed with water and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue

purified by flash chromatography on silica gel. Elution with EtOAc-cyclohexane (2:3) gave *the title compound* (5.234g). LCMS RT = 4.10min.

iii) (1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-({6-[(4-methyl-4-phenylpentyl)oxy]hexyl}amino)ethanol

A solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[(4-methyl-4-phenylpentyl)oxy]hexyl}-1,3-oxazolidin-2-one (5.23g) in THF (100ml) under nitrogen was treated with $KOSiMe_3$ (5.266g) and the mixture heated to 70° for 4h. The mixture was cooled to 20° and phosphate buffer solution (pH 6.5, 50ml) and water (100ml) were added. The mixture was extracted with EtOAc, the extract dried (Na_2SO_4) and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel. Elution with DCM-EtOH-0.880 ammonia solution (100:8:1) then (50:8:1) gave *the title compound* (4.922g). LCMS RT = 2.99min.

iv) 2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(4-methyl-4-phenylpentyl)oxy]hexyl}amino)ethyl]phenol acetate

A solution of (1*R*)-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-({6-[(4-methyl-4-phenylpentyl)oxy]hexyl}amino)ethanol (95mg) in acetic acid (4ml) and water (2ml) was heated to 70° for 30min. The mixture was cooled to 20° and the solvent was evaporated *in vacuo* to give *the title compound* (95mg). LCMS RT = 3.02 min, ES +ve 444 $(MH)^+$.

Example 2

2-(Hydroxymethyl)-4-((1*R*)-1-hydroxy-2-{[6-(2-methyl-2-phenylpropoxy)hexyl]amino}ethyl)phenol acetate

i) (5R)-3-(6-Bromohexyl)-5-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (2.00g) (WO 02/066422) in DMF (60ml) under nitrogen was treated with sodium hydride (60% dispersion in mineral oil, 385mg) and the mixture stirred at 20° for 30min. A solution of 1,6-dibromohexane (4.94ml) was added and the mixture was stirred at 20° for 3h. Phosphate buffer solution (pH 6.5, 30ml) and water (150ml) were added and the mixture was extracted with Et_2O. The extract was washed with water and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue purified by flash chromatography on

silica gel. Elution with DCM then MeOH-DCM (1:50) gave the *title compound* (2.565g). LCMS RT = 3.71min.

ii) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-[6-(2-methyl-2-phenylpropoxy)hexyl]-1,3-oxazolidin-2-one

A solution of 2-methyl-2-phenylpropan-1-ol (160mg) (J. Org Chem 1982, 47, 2476-2479) in DMF (8ml) under nitrogen was treated with sodium hydride (60% dispersion in mineral oil, 47mg) and the mixture stirred at 20° for 15min. (5*R*)-3-(6-Bromohexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (400mg) was then added and the mixture was stirred at 20° for 5h. Phosphate buffer solution (pH 6.5, 15ml) and water (15ml) were added and the mixture was extracted with EtOAc. The extract was washed with water and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residue purified by flash chromatography on silica gel. Elution with EtOAc-petroleum ether (1:4) then (1:2) gave an oil which was further purified by preparative thin layer chromatography on a silica plate (20 x 20cm). Elution with isopropyl acetate-toluene (2:3) gave *the title compound* (100mg). LCMS RT = 3.92 min.

iii) (1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-{[6-(2-methyl-2-phenylpropoxy)hexyl]amino}ethanol

Prepared using methods similar to those described in Example 1iii) LCMS RT = 2.98min.

iv) 2-(Hydroxymethyl)-4-((1*R*)-1-hydroxy-2-{[6-(2-methyl-2-phenylpropoxy)hexyl]amino}ethyl)phenol acetate

Prepared using methods similar to those described in Example 1iv).
LCMS RT = 2.74min, ES +ve 416 $(MH)^+$.

Example 3

2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(4-phenylpentyl)oxy]hexyl}amino)ethyl]phenol acetate

i) {4-[(6-Bromohexyl)oxy]-1-methylbutyl}benzene

Prepared using methods similar to those described in Example 1i) using 4-phenylpentan-1-ol (J. Chem. Soc., Perkin Transactions 1, 1985, 1983-95). LCMS RT = 4.23min.

ii) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[(4-phenylpentyl)oxy]hexyl}-1,3-oxazolidin-2-one

Prepared using methods similar to those described in Example 1ii). LCMS RT = 4.00min.

iii) (1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-({6-[(4-phenylpentyl)oxy]hexyl}amino)ethanol

Prepared using methods similar to those described in Example 1iii) LCMS RT = 2.93min.

iv) 2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(4-phenylpentyl)oxy]hexyl}amino)ethyl]phenol

A solution of (1*R*)-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-({6-[(4-phenylpentyl)oxy]hexyl}amino)ethanol (53.8mg) in acetic acid (5ml) and water (2.5ml) was heated to 70° for 0.5h. The mixture was cooled to 20° and the solvent was evaporated *in vacuo* to give a residue. This was chromatographed on silica (Biotage™, 4g) eluting with DCM-MeOH-0.880 ammonia (120:8:1) to give the *title compound* (37.8mg). LCMS RT = 2.63min

v) 2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(4-phenylpentyl)oxy]hexyl}amino)ethyl]phenol acetate

A portion of 2-(hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(4-phenylpentyl)oxy]hexyl}amino)ethyl]phenol (18.9mg) was dissolved in acetic acid (2ml) and the solvent was evaporated *in vacuo* to give the *title compound* (20mg). LCMS RT = 2.73min ES +ve 430 $(MH)^+$.

BIOLOGICAL ACTIVITY

In vitro measurements of compound potency and intrinsic activity at the human Beta 1, 2 and 3 receptors.

Method 1

The potencies of the compounds of Examples 1 and 2 were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal). At the human beta 2 adrenoreceptor, compounds of said examples had IC_{50} values below 1 μM.

Method 2

Potency of compounds of the invention at the human beta 2, 1 and 3 receptors was also determined using Chinese hamster ovary cells co-expressing the human receptor with a reporter gene. Studies were performed using either whole cells or membranes derived from those cells.

The three beta-receptors are coupled *via* the Gs G-protein to cause a stimulation of adenylate cyclase resulting in increased levels of cAMP in the cell. For direct cAMP measurements either membranes or cells have been used with either the HitHunter enzyme fragment complementation kit (DiscoveRx) or the FP^2 fluorescence polarisation kit (Perkin Elmer) to quantify the levels of cAMP present. These assays provide a measure of agonist potency and intrinsic activity of the compounds at the various receptors.

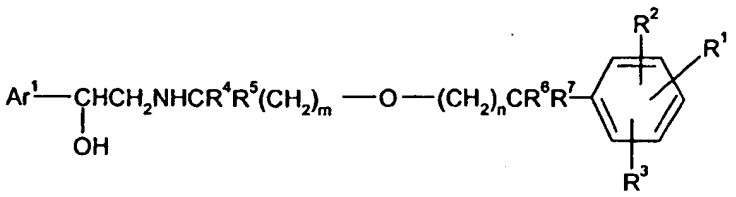
The reporter gene in the cells has also been used to quantify potency at the beta 1 and 3 receptors. This is a reporter of cAMP levels using the cAMP response element upstream of a firefly luciferase gene. After stimulation of the receptor with an agonist an increase in the level of luciferase is measured as a quantification of the level of cAMP in the cell.

In this assay the potency of compounds at the human beta-2 receptor is expressed as a pEC_{50} value.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. A compound of formula (I):



(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8; and
n is an integer of from 2 to 10,
with the proviso that m + n is 5 to 19;

R^1 is selected from hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6} alkoxy, cyano, nitro, halo, C_{1-6}haloalkyl, $-XNR^8C(O)R^9$, $-XNR^8C(O)NR^9R^{10}$, $-XNR^8C(O)NC(O)NR^9R^{10}$, $-XNR^8SO_2R^9$, $-XSO_2NR^9R^{10}$, XSR^8, $XSOR^8$, XSO_2R^8, $-XNR^9R^{10}$, $-XNR^8C(O)OR^9$, $XNR^8SO_2NR^9R^{10}$, XCO_2R^{10}, or $-XC(O)NR^9R^{10}$;
or R^1 is selected from -X-aryl, -X-hetaryl, or -X-(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, cyano, nitro, $CONR^9R^{10}$, $-NR^8C(O)R^9$, SR^8, SOR^8, $-SO_2R^8$, $-SO_2NR^9R^{10}$, $-CO_2R^{10}$, $-NR^9R^{10}$, or hetaryl optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, or C_{1-6}haloalkyl;

X is $-(CH_2)_r-$ or C_{2-6} alkenylene;

r is an integer from 0 to 6;

R^8 and R^9 are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6}alkyl)- and aryl(C_{1-6}alkyl)- and R^8 and R^9 are each independently optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, $-NHC(O)(C_{1-6}$alkyl), $-SO_2(C_{1-6}$alkyl), $-SO_2$(aryl), $-CO_2H$, and $-CO_2(C_{1-4}$alkyl), $-NH_2$, $-NH(C_{1-6}$alkyl), aryl(C_{1-6}alkyl)-, aryl(C_{2-6}alkenyl)-,

aryl(C_{2-6}alkynyl)-, hetaryl(C_{1-6}alkyl)-, -$NHSO_2$aryl, -NH(hetarylC_{1-6}alkyl), -$NHSO_2$hetaryl, -$NHSO_2$(C_{1-6}alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

or R^8 and R^9, together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered nitrogen – containing ring;

or where R^1 is $-XNR^8C(O)NR^9R^{10}$, R^8 and R^9 may, together with the -NC(O)N- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring;

or where R^1 is $-XNR^8C(O)OR^9$, R^8 and R^9 may, together with the -NC(O)O- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring;

R^{10} is selected from hydrogen, C_{1-6}alkyl and C_{3-7}cycloalkyl;

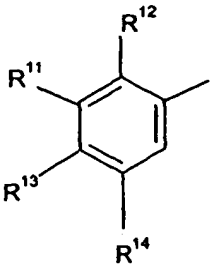
or where R^1 contains a moiety $-NR^9R^{10}$, R^9 and R^{10} may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

R^2 and R^3 are each independently selected from hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy, halo, aryl, aryl(C_{1-6}alkyl)-, C_{1-6}haloalkoxy, and C_{1-6}haloalkyl;

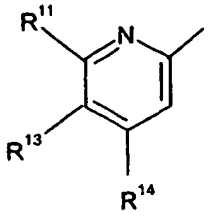
R^4 and R^5 are independently selected from hydrogen and C_{1-4}alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4;

one of R^6 and R^7 represents hydrogen or C_{1-4}alkyl and the other of R^6 and R^7 represents C_{1-4}alkyl, or R^6 and R^7, together with the carbon atom to which they are bonded, form a C_{3-7}cycloalkyl ring; and

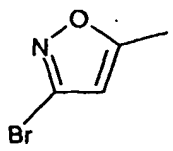
Ar^1 is a group selected from



(a)

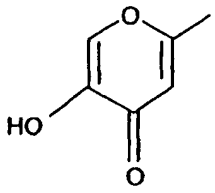


(b)



(c)

and



(d)

wherein R^{11} represents hydrogen, halogen, $-(CH_2)_qOR^{15}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}SO_2R^{16}$, $-SO_2NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$,

and R^{12} represents hydrogen, halogen or C_{1-4} alkyl;

or R^{11} represents $-NHR^{18}$ and R^{12} and $-NHR^{18}$ together form a 5- or 6- membered heterocyclic ring;

R^{13} represents hydrogen, halogen, $-OR^{15}$ or $-NR^{15}R^{16}$;

R^{14} represents hydrogen, halogen, haloC_{1-4} alkyl, $-OR^{15}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $-OC(O)NR^{15}R^{16}$;

R^{15} and R^{16} each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$ and $-OC(O)NR^{15}R^{16}$, R^{15} and R^{16} independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

R^{17} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

q is zero or an integer from 1 to 4.

2. A compound of formula (I) as defined in claim 1, or a salt, solvate or physiologically functional derivative thereof, except that R^{11} is not hydrogen.

3. A compound according to claim 1 or claim 2 wherein R^1 is selected from hydrogen, $XNR^8(CO)NR^9R^{10}$ or $-XSO_2NR^9R^{10}$, wherein X, R^8, R^9 and R^{10} are as defined in claim1.

4. A compound according to any of claims 1 to 3 wherein R^4 and R^5 are independently selected from hydrogen and methyl.

5. A compound according to any of claims 1 to 4 wherein one of R^6 and R^7 is selected from hydrogen and methyl, and the other of R^6 and R^7 represents methyl.

6. A compound according to any of claims 1 to 5 wherein m is 4, 5 or 6 and n is 2, 3, 4 or 5.

7. A compound according to any of claims 1 to 6 wherein Ar is selected from a group of structure (a) or (b) as defined in claim 1.

8. A compund of formula (I) selected from:
2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(4-methyl-4-phenylpentyl)oxy]hexyl}amino)ethyl]phenol;
2-(Hydroxymethyl)-4-((1*R*)-1-hydroxy-2-{[6-(2-methyl-2-phenylpropoxy)hexyl]amino}ethyl)phenol; or
2-(Hydroxymethyl)-4-[(1*R*)-1-hydroxy-2-({6-[(4-phenylpentyl)oxy]hexyl}amino)ethyl]phenol
or a salt, solvate or physiologically functional derivative thereof.

9. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated, which

comprises administration of a therapeutically effective amount of a compound of formula (I) according to any of claims 1 to 8 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

10. A compound of formula (I) according to any of claims 1 to 8 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

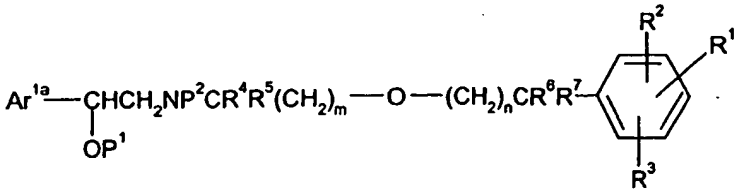
11. A pharmaceutical formulation comprising a compound of formula (I) according to any of claims 1 to 8 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

12. A combination comprising a compound of formula (I) according to any of claims 1 to 8 or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and one or more other therapeutic ingredients.

13. The use of a compound of formula according to any of claims 1 to 8, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist is indicated.

14. A process for the preparation of a compound of formula (I) according to any of claims 1 to 8 or a salt, solvate, or physiologically functional derivative thereof, which comprises:

(a) deprotection of a protected intermediate, for example of formula (II):

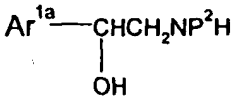


(II)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 m, and n are as defined for the compound of formula (I), Ar^{1a} is a protected form of Ar^1 and P^1 and

P^2 are each independently either hydrogen or a protecting group provided that at least one of Ar^{1a}, P^1 and P^2 is or contains a protecting group;

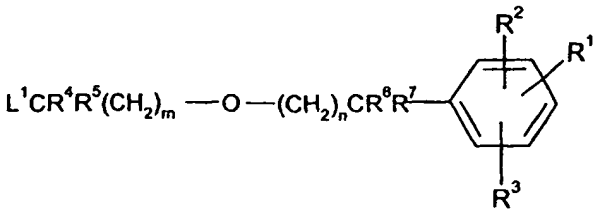
(b) alkylation of an amine of formula (X)



(X)

wherein Ar^{1a} is an optionally protected form of Ar^1 and P^2 is either hydrogen or a protecting group, provided that at least one of Ar^{1a} and P^2 is or contains a protecting group;

with a compound of formula (VI):



(VI)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 m, and n are as defined for the compound of formula (I) and L^1 is a leaving group;

followed by the following steps in any order:

(i) optional removal of any protecting groups;

(ii) optional separation of an enantiomer from a mixture of enantiomers;

(iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

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(74) Agent: **FLORENCE, Julia, Anne**; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

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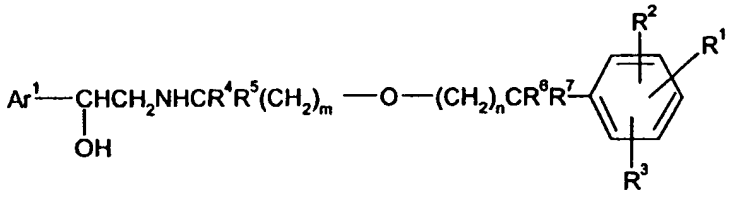
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHENETHANOLAMINE DERIVATIVES



(I)

(57) Abstract: The present invention relates to novel compounds of formula (I), to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use in the prophylaxis and treatment of respiratory diseases.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/12038

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C217/10 A61K31/137 A61P11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 140 800 A (GLAXO GROUP LTD) 5 December 1984 (1984-12-05) cited in the application whole document	1-14
A	GB 2 230 525 A (GLAXO GROUP LTD) 24 October 1990 (1990-10-24) example 2	1-14
A	WO 95/19336 A (IOVIS BIOMEDICAL AND PHARMACEU ;BRON JAN (NL); STERK GEERT JAN (NL) 20 July 1995 (1995-07-20) example 23	1-14

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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 May 2004	01/06/2004

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/12038

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 9

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/12038

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